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Three-dimensional ultrasound imaging and measurement of nasal bone length, prenasal thickness and frontomaxillary facial angle in normal second- and third-trimester fetuses

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KEYWORDS: Down syndrome; frontomaxillary facial angle; nasal bone length; prenasal thickness; three-dimensional ultrasound; ultrasound marker

ABSTRACT

Objectives To assess the feasibility of nasal bone length (NBL), prenasal thickness (PT) and frontomaxillary facial (FMF) angle measurements performed on the same three-dimensional (3D) multiplanar-corrected profile view in healthy second- and third-trimester fetuses, to create reference ranges and to review published measurement techniques.

Methods 3D volumes of 219 healthy second- and third-trimester fetuses were retrospectively analyzed. The quality of images and measurability of the markers were assessed with 5-point and 3-point scoring systems, respectively. Measurements of NBL (with care to exclude the frontal bone), PT and FMF were obtained in the exact mid-sagittal plane. Reference ranges were constructed based on measurements from images with high-quality (4 or 5 points) and high measurability (2 or 3 points) scores and compared with those in the most relevant published literature.

Results A high-quality score was assigned to 111 images. Among these, a high measurability score was significantly more often achieved for NBL (98.2%) and PT (97.3%) than for the FMF angle (26.1%) ($P < 0.001$). Both NBL ($NBL = -6.927 + (0.83 \times GA) - (0.01 \times GA^2)$) and PT ($PT = (0.212 \times GA) - 0.873$) (where GA = gestational age) showed growth with gestation, with less pronounced growth for NBL after 28 weeks. Our reference range for the NBL showed a systematically smaller length than those in other two-dimensional (2D) ultrasound-based publications. The FMF angle measurements that we obtained did not show a significant change with GA.

Conclusions NBL and PT are easily measured using 3D ultrasound whereas FMF angle measurement is more

challenging. When it is measured in the exact mid-sagittal plane and care is taken to exclude the frontal bone, measurements of the NBL are systematically smaller than those in previous 2D ultrasound-based publications. Copyright © 2012 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Down syndrome is characterized by specific facial features such as a flat face and a small nose¹. Continuous technical improvements in ultrasound techniques have enabled optimal visualization of these features which, in turn, have evolved into markers currently used as screening tools for the detection of Down syndrome. First-trimester nasal bone assessment, in combination with nuchal translucency measurements, was the first to be introduced², while second-trimester markers have also been proposed^{3–5}. Nasal bone length (NBL), prenasal thickness (PT) and the frontomaxillary facial (FMF) angle are three second-trimester markers measurable in the mid-sagittal profile view.

Improvements in three-dimensional (3D) ultrasound imaging have increased the accuracy of measurements by standardizing the examination plane through multiplanar correction of the acquired volume. The mid-sagittal plane obtained can differ considerably from the plane judged as mid-sagittal on two-dimensional (2D) ultrasound⁶. This has raised the question of whether the first published reference ranges, based on 2D images, are still valid and how they compare with the new ones obtained by 3D techniques. Reports on the role of 3D ultrasound in obtaining accurate NBL, PT and FMF angle measurements and individual reference ranges for these markers in the second trimester of pregnancy are available^{7–10}; however,

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no study has thus far measured all three markers in the same fetus and extended the normal ranges to the third trimester. Although screening programs for trisomies are offered earlier in pregnancy, late diagnosis of chromosomal anomalies is not uncommon, especially in countries with a low uptake of screening programs. In addition, even when termination of pregnancy is no longer an option, the diagnosis of Down syndrome can be of value in establishing the optimal place of delivery and optimal perinatal management, and in preparing parents for the birth of a Down syndrome baby.

The aims of this study were to assess the feasibility of NBL, PT and FMF angle measurements performed on the same 3D-corrected profile view in normal second- and third-trimester fetuses and to create reference ranges for these parameters. Furthermore, differences in definition or measurement techniques in the most relevant published literature on the individual markers were reviewed.

METHODS

The ultrasound unit of the Saint Antonius Hospital in Nieuwegein, The Netherlands, offers routine ultrasound investigation in the second and third trimesters of pregnancy. 3D images of the fetal face were collected cross-sectionally in 219 fetuses from a cohort of non-smoking, healthy, low-risk Caucasian women with a singleton pregnancy. Only non-anomalous fetuses from uncomplicated pregnancies were included. All images were obtained using a GE Voluson 730 Expert ultrasound system equipped with a RAB2-5L or RAB4-8L probe (GE Medical Systems, Kretz Ultrasound, Zipf, Austria). Volumes were acquired from fetuses facing the transducer, starting from as close as possible to the exact mid-sagittal profile view during periods of quiescence and with an insonation angle of less than 45°. An attempt was made to collect at least two such volumes per fetus. The volumes were stored on removable digital media for subsequent analysis on 4D View software version 7.0 (GE Medical Systems). These images were retrieved retrospectively for the purpose of this study and the markers measured offline using the multiplanar mode of the 4D View program. The study was approved by the local ethics committee and all women gave written consent.

Initially the multiplanar images were magnified to obtain the maximum possible size of the fetal profile, and the reference dot was positioned in Plane A (Figure 1a, upper left) just below the nasal bone. Planes B and C were then individually rotated to obtain symmetrical views of the orbits. When this multiplanar correction was carried out appropriately, the nasal bones and frontal processes of the maxilla automatically appeared in Plane B as an 'inverted V-shape'. To obtain an exact mid-sagittal view in Plane A, the reference dot was placed in Planes B and C exactly at an equal distance from the inner border of the orbits, at the level of the nasal bone. The adjusted planes, resulting in an exact mid-sagittal view in Plane A, are displayed in Figure 1a. NBL, PT and FMF angle were all measured in the enlarged image in Plane A.

For each fetus, the volume with the best mid-sagittal view was selected. Firstly, all images were corrected by multiplanar mode to the exact mid-sagittal view and scored from 1–5 in terms of quality for contrast and clarity (quality score), 1 being poor and 5 excellent. Specific points of interest were an optimal mid-sagittal view and clear contrast between the fetal profile and surrounding tissue or fluids. Only images with a quality score of 4 or 5 were used for further analysis. Subsequently, in the included images, each individual marker was scored from 1–3 in terms of visualization of landmarks (measurability score), 1 being poor and 3 excellent. Optimal contrast between bony and soft tissue at the location of the landmarks was considered important. Only markers with a measurability score of 2 or 3 were used for further analysis. Each marker was measured three times and the average was taken as the final measurement.

The nasal bone was measured from the nasion to the distal end of the white ossification line (Figure 1b). The nasion was defined as the most anterior point at the junction between the frontal and nasal bones. As the frontal bone extends posteriorly of the nasal bone (Figure 1c), care must be taken to measure the nasal bone starting from the level of the nasion, without including the frontal bone in the measurement, as this would erroneously enlarge the measured NBL (Figure 1d). The PT was measured as the shortest distance between the nasion (same landmark as used for measuring the NBL) and the frontal skin (Figure 1b). In cases in which there was a gap between the nasal and the frontal bones (disjunction), for PT measurement the landmark nasion was set at the point of intersection of two lines drawn tangentially to the nasal bone and to the lower part of the frontal bone, whereas for NBL measurements only the white ossified part of the nasal bone was measured.

The FMF angle was measured according to the different techniques proposed in the literature by various researchers; Sonek *et al.*⁵ measured the FMF angle with the first ray drawn from the top edge of the palatal complex (Figure 1e) and the second line to either the frontal bone or the skin anteriorly of the frontal bone. In contrast, Molina *et al.*⁷ made a distinction between two structures in the palatal complex: the vomer and the palate (Figure 1f). They placed the first ray along the palate and the second ray along the frontal bone. To determine which of these methodologies for FMF angle measurement was the easier to perform and more reproducible, we measured the FMF angle in six different ways (Figures 1e and f).

To assess intraobserver variability, all markers were remeasured in the acquired volumes following a 1-week interval. Interobserver variability was assessed by a second sonologist, who repeated the measurements as described above on all markers. Finally, results were compared with the most relevant literature. Data analysis was performed by Microsoft Excel for Windows 2000 (Microsoft Corp., Redmond, WA, USA) and SSPS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are presented as mean (SD) or median (range). Bland–Altman analysis was used

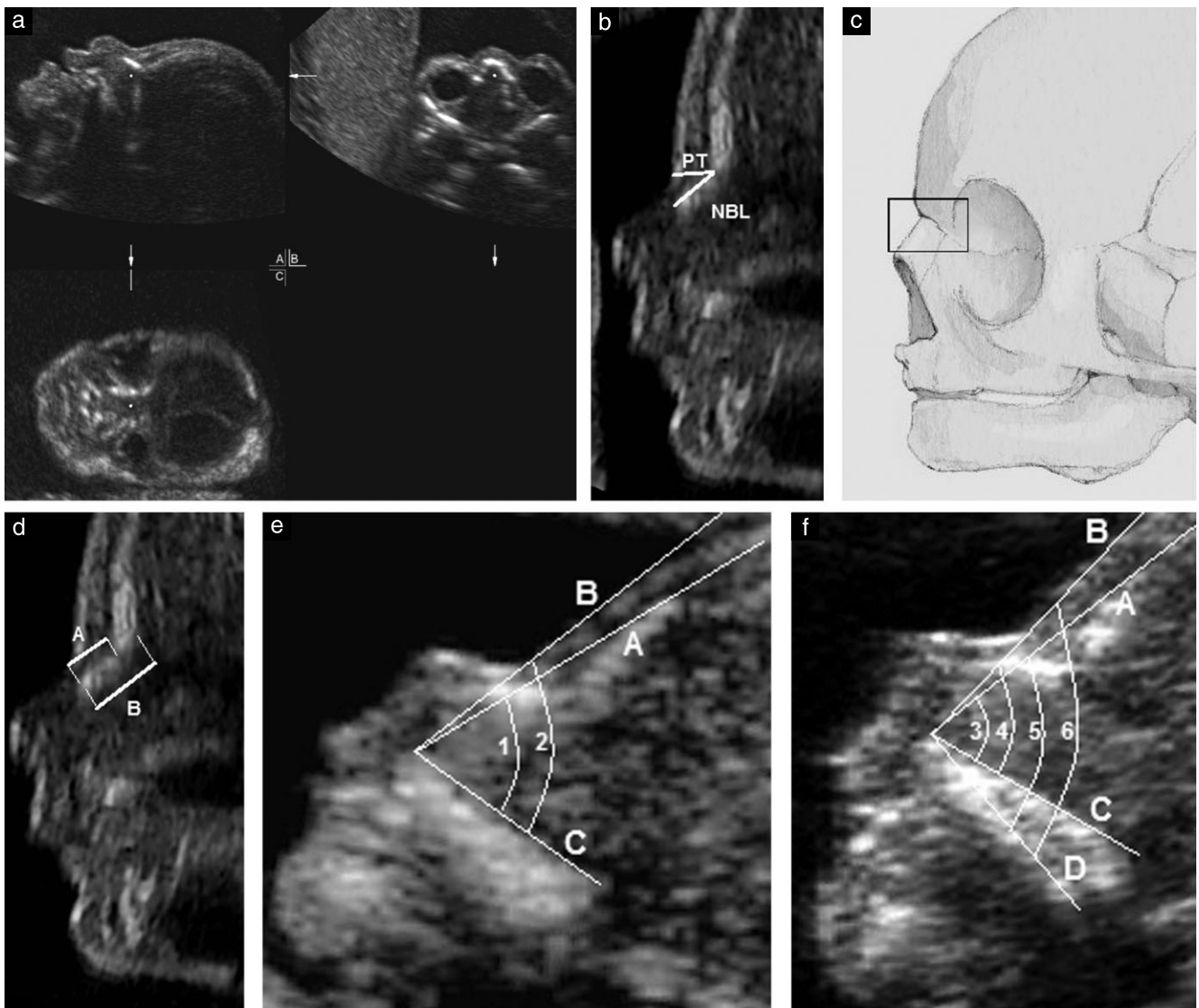


Figure 1 (a) Multiplanar ultrasound image showing the 'inverted V-form' of the nasal bones and frontal processes of the maxilla in Plane B. In Plane A the reference dot was placed just below the nasal bone and in both Planes B and C exactly at equal distances from the inner borders of the orbits. (b) Ultrasound image showing prenasal thickness (PT) and nasal bone length (NBL) measurements. (c) Illustration of the fetal skull: the frontal bone continues posteriorly to the nasal bone. (d) Ultrasound image showing correct NBL measurement (A) and incorrect NBL measurement with inclusion of the frontal bone (B). (e) Ultrasound image of measurement of frontomaxillary facial angles between the frontal bone (A), skin (B) and palatal complex (C). In cases where only the palatal complex was visible (and no distinction was possible between vomer and palate) the first ray was drawn along the upper surface of the palatal complex. The second ray was directed to either the frontal bone (angle 1, complex–bone) or skin (angle 2, complex–skin) at the point of its greatest anterior excursion. In all cases the point of intersection was the upper corner of the anterior aspect of the maxilla. (f) Ultrasound image of measurement of frontomaxillary facial angles between the frontal bone (A), skin (B), vomer (C) and palate (D). In cases where the two structures, vomer and palate, could be identified, the first ray was drawn along the upper surface of the vomer or through the palate. The second ray was directed to either the frontal bone or skin at the point of its greatest anterior excursion. In all cases the point of intersection was the upper corner of the anterior aspect of the maxilla. 3, vomer–bone angle; 4, vomer–skin angle; 5, palate–bone angle; 6, palate–skin angle.

to describe intra- and interobserver variability. The best-fit polynomial line was used for constructing reference ranges. Differences between observed frequencies were compared by the chi-square test, and $P < 0.05$ was considered to be statistically significant.

RESULTS

The cross-sectional study group included 219 fetuses at 15–33 weeks' gestation (mean, 23 weeks). In 111 fetuses the mid-sagittal image obtained was given a quality score

of 4 or 5. The quality scores of the images from all 219 fetuses and the measurability scores of the 111 high-quality images are presented in Table 1. The frequency distribution of the measurability scores of the 111 high-quality images was not equal for the three markers (chi-square $P < 0.001$). A measurability score ≥ 2 was obtained in 109 cases for the NBL (98.2%), in 108 cases for the PT (97.3%) and in 29 cases for the FMF angle (26.1%). A measurability score of ≥ 2 was obtained for both NBL and PT measured in the same mid-sagittal profile view in 106 cases (95.5%), for FMF angle and

Table 1 Quality score of 219 images and measurability score of facial markers in 111 images that had a quality score of 4 or 5

Score	Quality (n = 219)	Measurability (n = 111)		
		NBL	PT	FMF
1	7	2	3	82
2	47	105	102	28
3	54	4	6	1
4	108	—	—	—
5	3	—	—	—

Data given as number of images. Quality was scored from 1 (poor) to 5 (excellent) for contrast and clarity. Measurability was scored from 1 (poor) to 3 (excellent) in terms of visualization of landmarks. FMF, frontomaxillary facial angle; NBL, nasal bone length; PT prenasal thickness.

NBL in 26 cases (23.4%) and for FMF angle and PT in 28 cases (25.2%). The angle between the transducer and the nasal bone was less than 45° in all cases.

The intraobserver 95% limits of agreement were −1.03 to 0.86 mm, −0.61 to 0.76 mm and −8.18 to 5.29°, for NBL, PT and FMF angle, respectively. The respective interobserver 95% limits of agreement were −1.20 to 1.30 mm, −0.52 to 0.69 mm and −6.22 to 8.50° (Table 2).

NBL increased significantly with gestational age (GA), from 3.3 mm at 15 weeks' gestation to 9.6 mm at 33 weeks (linear regression $P < 0.001$). NBL followed a second order polynomial relationship with GA: $NBL = -6.927 + (0.83 \times GA) - (0.01 \times GA^2)$ ($R^2 = 0.78$, $P < 0.001$) (Figure 2). Figure 2 also shows the mean NBL derived from this study compared with the mean published by Sonek *et al.*¹¹.

PT increased significantly with GA from 2.3 mm at 15 weeks to 6.1 mm at 33 weeks (linear regression $P < 0.001$). A linear relationship with GA was confirmed on polynomial regression: $PT = (0.212 \times GA) - 0.873$ ($R^2 = 0.74$, $P < 0.001$) (Figure 3). A comparison between the mean PT derived from this study and mean PT measured by Persico *et al.*⁹ is also shown in Figure 3.

The palate and vomer were seen as a palatal complex in 21 out of 29 cases (72.4%), and as two separate structures in eight cases (27.6%). The likelihood of the two being observed as a palatal complex or as two separate structures seemed to be independent of GA. Median GA for visualization as a palatal complex was 19.5 (range,

15.4–28.2) weeks, and for separate structures it was 18.5 (range, 15.6–25.5) weeks. In view of the paucity of FMF angle data, the measurements of 'complex' angles (angles 1 and 2, Figure 1e) and 'vomer' angles (angles 3 and 4, Figure 1f) were pooled together; given the fact that in both measurements the first ray is placed at the same position, the angles 'complex–bone' and 'vomer–bone' are similar, as are 'complex–skin' and 'vomer–skin'. The difference between FMF angles measured to the skin or to the bone had a constant value of 10° (median 10.0°, range 6.1–14.6°) throughout gestation (Pearson's $r = -0.12$, $P = 0.54$), making it unnecessary to use these two different measurement techniques in this study. Consequently, further analysis of FMF angles was performed by analyzing two measurements only: complex/vomer–bone angle (i.e. complex–bone and vomer–bone pooled together) and palate–bone angle (Figure 4). The FMF angles did not change significantly with gestation, with a mean complex/vomer–bone value of 67.05° (range, 57.85–77.78°; $SD = 4.34$) ($P = 0.11$). The mean palate–bone angle was 85.08° (range, 80.8–94.9°; $SD = 5.13$) ($P = 0.74$).

NBL and PT were highly correlated ($P < 0.001$). Owing to the paucity of FMF angle data, no analysis of correlation was performed between this and any other marker.

DISCUSSION

In this study we present novel reference ranges for NBL and PT measured on multiplanar view-corrected mid-sagittal plane using 3D volumes of normal second- and third-trimester fetuses. Both NBL and PT showed growth with gestation, with less pronounced growth for NBL after 28 weeks. Good visualization leading to high-quality measurements was achieved significantly more often for NBL and PT than for the FMF angle.

To the best of our knowledge this is the first study using 3D ultrasound to measure all three markers in the same fetus and extending the measurements into the third trimester.

Markers for Down syndrome are mainly studied early in pregnancy. However, uptake of first-trimester screening varies across countries as well as does the rate of late bookers. It is therefore important to have effective Down syndrome markers available for later diagnosis in pregnancy.

Table 2 Intra- and interobserver mean differences and 95% limits of agreement (LOA) with 95% CIs between paired measurements of facial markers

Measurement	Intraobserver		Interobserver	
	Mean diff.	LOA (95% CI)	Mean diff.	LOA (95% CI)
NBL (mm)	−0.08	−1.03 (−0.87, −1.19), 0.86 (0.71, 1.02)	0.05	−1.20 (−0.99, −1.40), 1.30 (1.09, 1.50)
PT (mm)	0.08	−0.61 (−0.49, −0.72), 0.76 (0.65, 0.88)	0.09	−0.52 (−0.62, −0.42), 0.69 (0.59, 0.79)
FMF (°)	−1.45	−8.18 (−5.98, −10.38), 5.29 (3.08, 7.49)	1.14	−6.22 (−3.85, −8.59), 8.50 (6.13, 10.87)

Diff., difference; FMF, frontomaxillary facial angle; NBL, nasal bone length; PT, prenasal thickness.

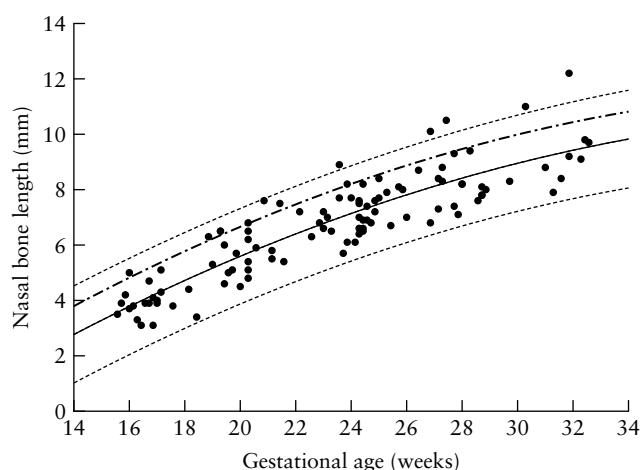


Figure 2 Scatterplot of nasal bone length (NBL) with mean (—) and 5th and 95th percentiles (----) in 109 healthy fetuses, showing mean NBL from reference range of Sonek *et al.*¹¹ (· · · · ·).

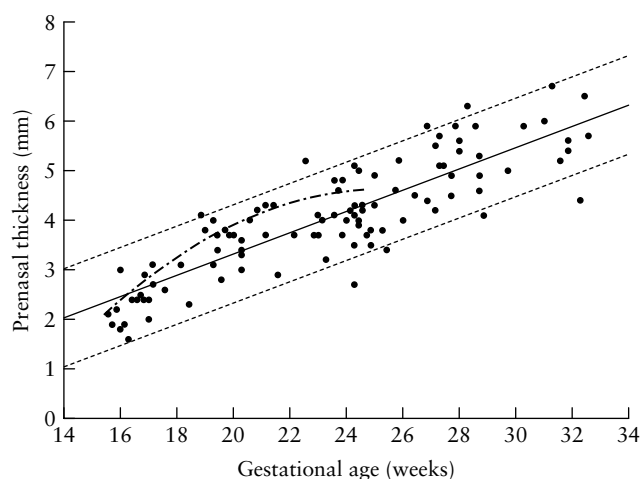


Figure 3 Scatterplot of prenatal thickness (PT) with mean (—) and 5th and 95th percentiles (----) in 108 healthy fetuses, showing mean PT from reference range of Persico *et al.*⁹ (· · · · ·).

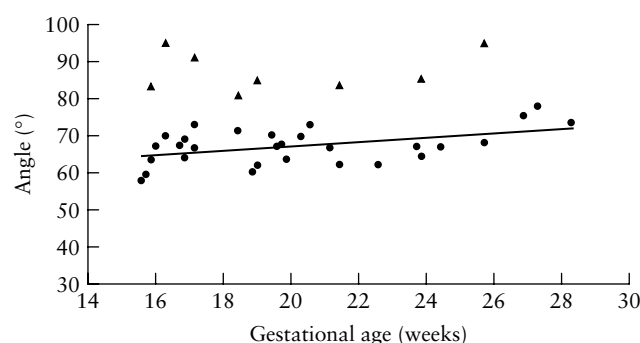


Figure 4 Scatterplots of palate–bone angle measurements (▲) in eight fetuses and of complex/vomer–bone angle measurements (●) with corresponding mean trend in 29 fetuses ($P = 0.11$).

The importance of measuring NBL, PT and FMF angle in the exact mid-sagittal view has recently been emphasized in the literature by a study showing that the use of 3D multiplanar mode improves the accuracy of profile

measurements⁶. In addition, Persico *et al.*¹⁰ showed that the NBL is overestimated when measured in oblique mid-sagittal views and underestimated in parasagittal planes.

Although the present study design was retrospective, volumes were rigorously selected in order to obtain optimal measurements. The stored volumes did not always allow optimal visualization of facial structures to enable high-quality measurements. This was dependent on the angle of insonation and fetal position. Although this may seem a limitation of the study, in our opinion it rather reflects a ‘real-world’ situation where, in a routine clinical setting, volumes are stored during the examination and markers measured retrospectively.

Measurement of the FMF angle was particularly challenging, being judged to be of high quality only in 26% of the cases, in contrast to 98% and 97% for NBL and PT, respectively. This suggests that measurement of the FMF angle is more difficult after the first trimester and probably requires a very specific insonation angle to avoid shadowing by the facial bony structures that hamper good visualization of the thin vomer.

After re-examining the nasal and frontal bones on multiplanar mode-corrected profile view using 3D volumes, we redefined our measurement technique. In the new technique care was taken not to add part of the frontal bone to the measurement of the NBL, as this would erroneously increase the measurement (Figures 1c and d). When in Down syndrome fetuses the nasal bone is hypoplastic, the nasal and frontal bones are not in contact, but are separated by a gap (nasal bone–frontal bone disjunction). In such cases we used the reconstructed landmark nasion as a starting point for PT measurement, instead of the lowest part of the frontal bone. This landmark may be more difficult to reconstruct in case of absence of the nasal bone in the second and third trimesters of pregnancy. However, later in pregnancy the nasal bone is more commonly hypoplastic rather than absent. We preferred to measure PT from the (landmark) nasion, as this avoids combining bony tissue and skin tissue in the PT measurement. The advantage would be that only the skin is measured, which tends in our opinion to be more edematous in Down syndrome fetuses. However, comparative studies are needed to substantiate this assumption.

It is mandatory to adhere to standardized measurement techniques when using markers for the estimation of Down syndrome risk in order to prevent overestimation or underestimation of the calculated risk. Several measurement techniques for NBL have been described in the literature (Table S1 online)^{3,8,10–12}. 2D ultrasound may lead to overestimation of the NBL if this is measured slightly obliquely and/or the measurement erroneously includes part of the frontal bone. This supposition is confirmed by the smaller NBL in our study and in that of Persico *et al.*¹⁰. Moreover, when our range is compared with the 2D reference range published by Sonek *et al.*¹¹, the NBL in our study is systematically smaller (by about 1–2 mm) while the means otherwise follow the same trend (Figure 2).

Both Maymon *et al.*^{4,13} and Persico *et al.*⁹ studied PT in normal fetuses. We chose to compare our results with

those of the latter study, as it is recent and based entirely on 3D-corrected images examined offline. While our results show a linear trend of PT with GA, the reference range of Persico *et al.* follows a second-order polynomial trend. Possible explanations for this discrepancy could be that our study has a wider gestational window (15–33 compared with 16–24 weeks) and that we used a different definition of PT in cases of disjunction. Nevertheless it seems unlikely that this different definition could play a major role in explaining the discrepancy between reference ranges, as disjunction was observed in only a very limited number of cases.

For FMF angle measurement we used six different techniques (Figure 1e and f) that have been described previously in the literature. The difference between the FMF angles using a ray towards the frontal bone or the frontal skin showed a non-significant change between 15 and 33 weeks' gestation, with a mean of 10°. We observed that (independently of GA) in our population the vomer and palate were more often seen as one complex than as two separate structures. For these reasons we decided to adopt the combination complex–bone/vomer–bone angle and the palate–bone angle. Of the three facial measurements we found the FMF angle to be the most difficult to visualize and measure.

FMF angle measurement in normal second-trimester fetuses has previously been performed by Sonek *et al.*⁵ and Odibo *et al.*¹⁴ using 2D ultrasound and by Molina *et al.*⁷ using 3D ultrasound. Consistent with the findings of Molina *et al.* and in contrast to those of Sonek *et al.* and Odibo *et al.*, our results show a constant FMF angle measured from the palate and a slight increase in the FMF angle measured from the vomer through gestation (Figure 4), although the latter was not statistically significant, possibly due to the small number of cases.

In conclusion, when measured on 3D volumes, NBL and PT are reproducible markers and easy to measure, whereas the FMF angle is more challenging. In this study we present novel reference ranges for NBL and PT. Both NBL and PT show growth with gestation, with less pronounced growth for the NBL after 28 weeks. Following measurement in the exact mid-sagittal plane and with care taken to exclude the frontal bone, our reference range for the NBL showed a systematically smaller length than those in other publications.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:



Table S1 Overview of definitions used for nasal bone length, prenasal thickness and frontomaxillary facial angle.

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